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Sustained drug release from ultrathin hydrogel film

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We reported a facile method to prepare camptothecin (CPT) loaded ultrathin hydrogel films based on a polymeric prodrug via layer by layer (LbL) thiol-ene "click" chemistry. Free camptothecin could be sustainedly released from the ultrathin hydrogel film within 24 hours through the hydrolysis of ester bonds between hydrogel backbone and camptothecin moieties.

Sustained release of drugs from the surfaces of medical devices has long been thought to provide a unique method of local and regional drug delivery.[1] Many efforts have been given to prepare ultrathin drug-loaded coatings on medical devices.[2]

Hydrogels are three-dimensional polymer networks that are able to retain a large fraction of water in their structure, which is similar to natural living tissue more than any other synthetic biomaterials.[3] Ultrathin hydrogel films are capable of fast response and show widespread practical value, and have been paid much attention due to their promising applications on sensing, advanced delivery and external functionalization of materials,[4-8] which is opening a new field of modification and improvement of the surface characteristics for application in various fields.

Usually, ultrathin hydrogel films could be prepared by spin-casting with hydrogel precursors, and subsequent crosslinking.[9] However, spin-casting can only fabricate hydrogel films on smooth surfaces, and is difficult to control the thickness of hydrogel films below micron scale.[10] Layer-by-layer (LbL) assembly technique is a facile way to fabricate multilayer or ultrathin films as the layer thickness can be controlled.[11-13] The most prominent advantage of LbL is the independence of the geometry of the initial surface. The classical concept of LbL is electrostatic self-assembly.[14, 15] Recently, LbL process driven by covalent bonds is being paid much attention, which can tailor surface properties of materials with defined properties.[16-19] In our previous work, we have reported a facile strategy to prepare ultrathin hydrogel films with controlled thickness via LbL technique and Michael addition type thiol-ene "click" chemistry using multifunctional poly(ethylene glycol) derivatives as precursors.[20] The LbL process was carried out under physiological conditions, which make it a suitable strategy to prepare ultrathin hydrogel coatings on medical devices.

Water insoluble drugs could be diffused into the hydrogels employing amphiphilic block polymers as precursors.[21, 22] However, because of the weak interactions between drug and hydrophobic segment, the stability and drug loading capacities of this kind of hydrogels are greatly limited. Alternatively, hydrophobic drugs could be covalently bonded onto the hydrophilic polymeric carriers to form water soluble polymer-drug conjugates[23], and use as hydrogel precursors, which can avoid the burst release and enhance drug loading capacity.

In the present study, poly[oligo(ethylene glycol) mercaptosuccinate] (POEGMS),[24, 25] a biodegradable poly(ethylene glycol) (PEG) derivative with multiple thiols, was first synthesized by polycondensation of oligo(ethylene glycol) diol and mercaptosuccinic acid using scandium trifluoromethanesulfonate [$Sc(OTf)_3$][26] as catalyst according our previous report. At the same time, camptothecin (CPT), a hydrophobic antitumor drug, was used as the model drug and modified by acryloyl chloride, resulting in acryl-CPT, a small molecular prodrug of CPT. Then partial thiols of POEGMS was reacted with acryl-CPT through thiol-ene "click" chemistry, to give a water soluble polymeric prodrug with numerous thiols and pendant CPT moieties (POEGMS-*g*-CPT). Poly[oligo(ethylene glycol) maleate] (POEGM)[27] with multiple unsaturated double bonds was synthesized by similar polycondensation procedure, which was used as hydrogel precursor with POEGMS-*g*-CPT to fabricate ultrathin hydrogel films via the LbL thiol-ene "click" chemistry on a silicon or quartz substrate (Scheme 1). The LbL "click" process could be conducted continuously in the PBS (pH 7.4). POEGM with multiple unsaturated double bonds first reacted with the thiols on the silicon or quartz substrate to form a single layer of polymer. Subsequently, the thiols of POEGMS-*g*-CPT reacted with the remaining double bonds of the immobilized POEGM on the substrate, to give the second layer.

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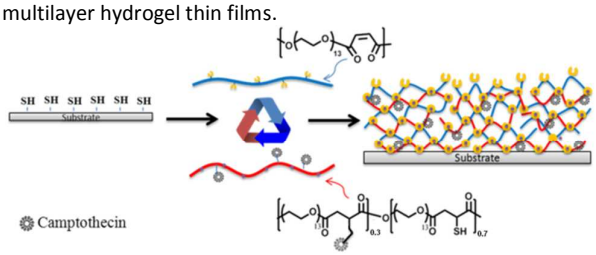
Repeated deposition of the polymers gave the corresponding multilayer hydrogel thin films.



Scheme 1 Fabricating CPT-loaded ultrathin hydrogel films via LbL thiol-ene "click" chemistry.

UV-vis absorption was used to monitor the process of multilayer fabrication. The quinolone ring of CPT moieties showed strong absorption of ultraviolet, so the intensity of the multilayer enhanced with increase of the CPT amount. Fig. 1 shows the UV-vis absorption spectra of different bilayers (from 1 to 10) on a quartz slide. The UV-vis absorption of the hydrogel films increased gradually with the number of bilayers, indicating a progressive reaction with almost an equal amount of the copolymers in each cycle. To further estimate the growth of the ultrathin hydrogel films, an ellipsometer was used to monitor the thickness of the hydrogel films upon bilayer numbers. As shown in Fig. 2 the ultrathin hydrogel films displayed a linear relationship between the thickness and bilayer numbers, which could be described as:

$d = 1.5412n + 7.3863$ ($R^2 = 0.987$)

, where d is the thickness of the hydrogel films and n is the number of bilayers. The result implied that the hydrogel films grow on the substrates in a consistent and constant manner with a regular thickness increase averaging 1.54 nm per bilayer. Combining the results of UV-vis absorption spectra and ellipsometer, the LbL "click" chemistry allows an excellent control over the hydrogel film thickness.

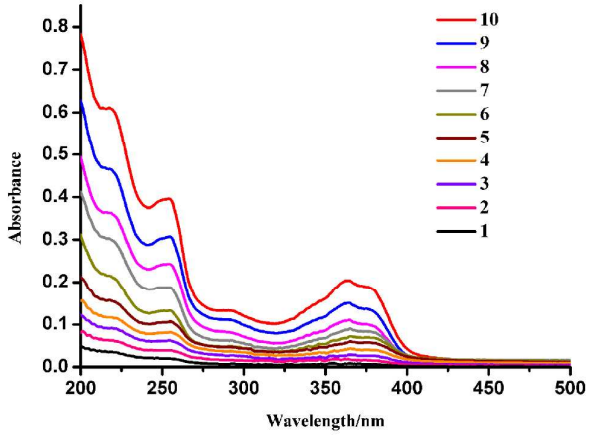


Fig. 1 UV- vis absorption spectra of the ultrathin hydrogel films on quartz with increasing bilayer numbers.

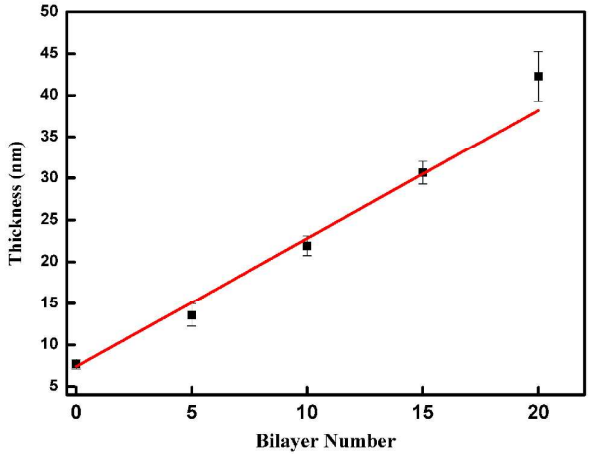


Fig. 2 Relationship between film thickness as determined by ellipsometer and number of bilayers for the ultrathin hydrogel film.

The silicon slides coated with 20-bilayer drug-loaded ultrathin hydrogel films were immersed into PBS solutions (10 mM, pH 7.4) at 37 °C to investigate the CPT release behavior. The CPT moieties were conjugated onto the hydrogel backbone through ester bonds, which can hydrolyze in aqueous media, to release free CPT molecules. Furthermore, the hydrolytic rate of ester bonds formed from tertiary hydroxyl groups was relatively faster than those from primary hydroxyl groups,[28] which indicates that the free CPT molecules were recovered from the hydrogel backbone and released into the aqueous media before the degradation of hydrogel thin film. Fig. 3 shows the CPT release profile from the ultrathin hydrogel films with 20 bilayers. Although the thickness of the hydrogel films was only tens of nanometers, a sustained release of CPT was observed within 24 hours with almost constant release rate. According to the accumulated release amount of CPT, the CPT loading density of 20-bilayer hydrogel film is about 0.22 μg/cm^2. Although the drug loading density is relatively low, the specific surface area of some medical devices with complex geometry is very large, which could improve the drug loading content. Furthermore, hydrogel thin films with hundreds or thousands of bilayers could be prepared using automatics for layer-by-layer deposition. The drug loading content may match the dose for clinical applications.

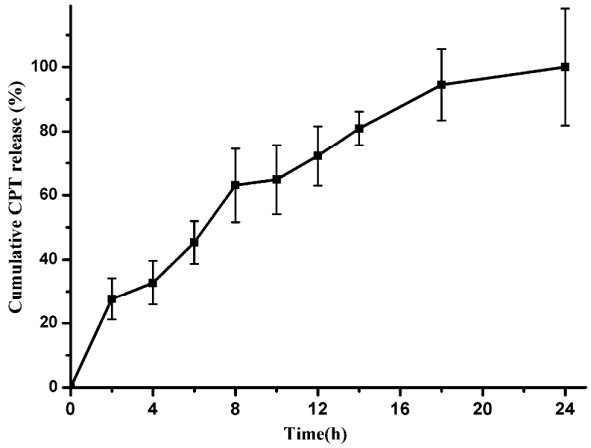


Fig. 3 *In vitro* CPT release profile from ultrathin hydrogel film at 37˚C and pH 7.4.

In conclusion, we have provided a facile strategy to prepare drug-loaded ultrathin hydrogel film on nonplanar surfaces using multifunctional water soluble polymeric prodrug as precursor via layer-by-layer thiol-ene "click" reaction. The thickness of the hydrogel film could be well controlled by the number of bilayers, and the loaded drug could be sustainedly released from the film through hydrolysis. This new strategy has potential to prepare implantable medical devices with drug-loaded coatings for localized drug delivery.

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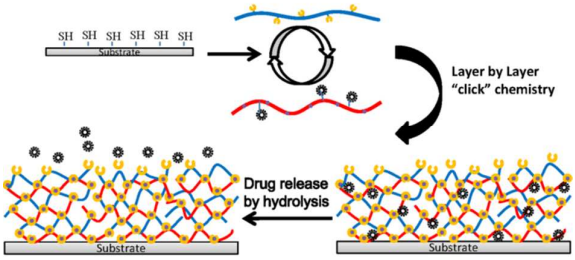
Graphic Abstract



We reported a facile strategy to prepare camptothecin-loaded ultrathin hydrogel film, which showed a sustained release of camptothecin in PBS.